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Affected by Prostate Cancer?



SUPPORT - EDUCATION - ADVOCACY

Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

Radiation-Hormone Combo Effective in Prostate Cancer

High-risk men with localized prostate cancer had improved biochemical disease-free survival (bDFS) when six months of androgen deprivation therapy (ADT) were combined with radiotherapy (RT). Moreover, the combination did not increase adverse effects, according to a randomized European Organisation for Research and Treatment of Cancer (EORTC 22991) trial reported online ahead of print in the *Journal of Clinical Oncology*.

At 7.2 years' median follow-

up, the study found that combination therapy led to a five-year bDFS of 82.6% (95% confidence interval [CI] 78.4-86.1) vs. 69.8% for RT alone (95% CI 64.9-74.2) – translating to a hazard ratio (HR) of 0.52 (95% CI 0.41-0.66, P=0.001, 319 events). Adjuvant ADT also improved clinical progression-free survival (cPFS), for an HR of 0.63 (95% CI 0.48-0.84, P=0.001, 205 events).

No statistically significant interaction between treatment effect and RT dose emerged: heterogeneity P=0.79 and P=0.66, for bDFS and PFS, respectively, ac-

ording to Michel Bolla, MD, of Grenoble University Hospital in France, and colleagues. "[F]or patients with low-volume high-risk localized prostate cancer, our results pave the way to using a combination approach with 78-Gy RT plus a short duration of ADT," the researchers wrote. They called for a study to compare short-term treatment with long-term or intermediate ADT.

The trial recruited 819 men with localized prostate cancer, median age 70 (43-80), recruited during 2001-2008

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For Prostate Cancer, More Radiation May Not Improve Survival

New technology has enabled doctors to administer higher doses of radiotherapy (RT) to prostate cancer patients with fewer side effects. However, a new study shows that escalating the dose may not actually help in the long term, at least not men with localized prostate cancer. The results were published online in the *American Journal of Clinical Oncology*.

"In the field of radiation oncology, we often assume that the highest dose that the body can tolerate will be most effective at killing cancer," says Dr. Robert Den, MD, a researcher at the Sidney Kimmel Cancer Center at Thomas Jefferson University and senior author on the paper. "Our results argue that this may not be the case, at least not with lower-risk prostate cancer patients."

Dr. Den, an associate professor of radiation oncology, cancer biology, and urology at Jefferson, and colleagues analyzed data from 12 randomized controlled trials of external beam RT (EBRT) for men with non-metastatic prostate cancer, which included a total of 6,884 patients. By pooling data from multiple clinical trials, the researchers were able to see trends that would not have been apparent in the individual studies.

Rather than use the typical proxy for patient improvement, the PSA test, the researchers looked at long-term outcomes such as the development of metastatic cancer and death from cancer. They found that while PSA levels decreased as patients received higher doses of RT, the overall survival and incidence of

(Continued on page 8)

Economic Analysis of PSA Screening, Selective Treatment Strategies

Can PSA screening for prostate cancer be cost-effective? A study, commentary and author interview published online by *JAMA Oncology* examines that question.

The future of PSA screening is uncertain with the US Preventive Services Task Force's (USPSTF) recommendation against routine PSA screening for prostate cancer and conservative guidance from other panels.

Ruth Etzioni, PhD, of the Fred Hutchinson Cancer Research Center in Seattle, WA, and coauthors used simulation modeling to examine the potential cost-effectiveness of plausible PSA screening strategies and to assess the value added by increased use of conservative management

among low-risk, screening-detected cancer cases. The study reports that if PSA screening is to be cost-effective, it should be used conservatively and combined with conservative management for low-risk disease.

"Our findings have clear implications for the future of PSA screening in the United States. Rather than stopping PSA screening, as recommended by the USPSTF, implementation of strategies that extend the screening interval and/or use higher PSA biopsy thresholds have the potential to preserve substantial benefit while controlling harm and costs," the article concludes.

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Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men with Castration-Resistant Prostate Cancer

Halibi S, Kelly WK, Ma H, et al

J Clin Oncol 7 March 2016; Epub before print

Purpose: Reports have suggested that metastatic site is an important predictor of overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC), but these were based on a limited number of patients. We investigate the impact of site of metastases on OS of a substantial sample of men with mCRPC who received docetaxel chemotherapy in nine phase III trials.

Patients and Methods: Individual patient data from 8,820 men with mCRPC enrolled onto nine phase III trials were combined. Site of metastases was categorized as lymph node (LN) only, bone with or without LN (with no visceral metastases), any lung metastases (but no liver), and any liver metastases.

any lung metastases (but no liver), and any liver metastases.

Results: Most patients had bone with or without LN metastases (72.8%), followed by visceral disease (20.8%) and LN-only disease (6.4%). Men with liver metastases had the worst median OS (13.5 months). Although men with lung metastases had better median OS (19.4 months) compared with men with liver metastases, they had significantly worse median survival duration than men with nonvisceral bone metastases (21.3 months). Men with LN-only disease had a median OS of 31.6 months. The pooled hazard ratios for death in men with lung me-

tastases compared with men with bone with or without LN metastases and in men with any liver metastases compared with men with lung metastases were 1.14 (95% CI, 1.04 to 1.25; P=0.007) and 1.52 (95% CI, 1.35 to 1.73; P<0.0001), respectively.

Conclusion: Specific sites of metastases in men with mCRPC are associated with differential OS, with successive increased lethality for lung and liver metastases versus bone and nonvisceral involvement. These data may help in treatment decisions, the design of future clinical trials, and understanding the variation in biology of different sites of metastases in men with mCRPC.

Enzalutamide Broadly Effective in Certain Prostate Cancers

The PREVAIL trial of enzalutamide (Xtandi®) showed the efficacy of the agent in chemotherapy-naive metastatic castration-resistant prostate cancer (CRPC). New examination of the data by multinational investigators confirms its benefit across subgroups.

As Dr. Christopher P. Evans stated by email, “The subset analysis of PREVAIL is consistent with the initial report and validates enzalutamide across the castration-resistant prostate cancer (CRPC) disease spectrum of location and extent of disease.”

In a March 20 online paper in *European Urology*, Dr. Evans, of the University of California, Davis, School of Medicine and colleagues note that the PREVAIL study randomized men with minimal or no CRPC symptoms to enzalutamide or placebo plus continued standard androgen deprivation therapy (ADT).

In this analysis, researchers examined data by subgroup. This included 1,513 men with nonvisceral disease, 204 with visceral disease, 867 with fewer than four bone metastases (low-volume bone disease), 850 with four or more bone metastases (high-volume bone disease) and 195 with lymph node-only disease.

Compared to placebo, enzalutamide improved radiographic progression-free survival in patients with nonvisceral disease (hazard ratio [HR] 0.18) and visceral disease (HR 0.28). This was also true in low- or high-volume bone disease (HR 0.16 and 0.22) and in lymph node only disease (HR 0.09).

For overall survival, the HR was below 1 across all disease subgroups and the agent was well tolerated in men with or without visceral disease. The incidence of adverse events leading to

discontinuation of the agent was 6% in both subgroups.

The results, the researchers concluded, “suggest that enzalutamide is an active treatment in this prostate cancer population, irrespective of the location and extent of baseline disease.”

Dr. James L. Mohler of Roswell Park Cancer Institute, New York, commented, “The benefits observed with enzalutamide compared to placebo across all CRPC subgroups confirm that prostate cancer remains androgen-sensitive probably due to its ability to produce testicular androgens by intratumoral, intracrine androgen metabolism.” But, he noted that the drug’s added benefit toward overall survival was short and he encouraged greater focus on the development of even better treatments for CRPC.

Reuters Health Information
7 April 2016

Doc Moyad's What Works & What is Worthless Column, Also Known As "No Bogus Science" Column

"More HOPE/Proof Than Ever That Statins Help Many Healthy People!"

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor's Note: Us TOO invites certain physicians and others to provide information and commentary for the *Hot SHEET* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

Bottom Line:

A new major randomized trial (in fact the largest international statin versus placebo trial in healthy men and women without heart disease) was just completed called the "HOPE 3" trial. And it demonstrated a reduction in the risk of heart attacks, strokes, the need for cardiovascular procedures like stents and bypass surgery, and even reduced the risk of cardiovascular deaths in just 5.6 years in the group taking just 10 mg of rosuvastatin (aka Crestor®) daily vs. placebo.¹ However, why wasn't there a basic lifestyle changes group also?!!! That is the real conspiracy!!!

It is interesting that before this major trial (called the "HOPE-3 trial") there were already 18 randomized trials and over 55,000 patients (ages 28 to 97 years) that showed a benefit for statins in primary prevention (aka healthy folks)! Now, this is

the most diverse trial ever recorded (21 countries, six continents and approximately 13,000 men and women) that continues to support what the previous 18 have demonstrated! Statins in lower risk non-cardiovascular diseased patients can save lives, reduce the risk of heart attack and stroke, and prevent invasive cardiovascular procedures and could potentially have no impact or reduce the risk of numerous cancers.

Why don't we have a phase 3 trial of statins to prevent aggressive prostate cancer or the recurrence of prostate cancer? I have waited almost two decades and published a plethora of articles on this and it is my HOPE (get it) this or the next generation of health care professionals/ researchers gets the answer to this question that should have been answered 10-20 years ago! I love all the statin conspiracy folks (probably the same group that still believes there was a gunman

on the grassy knoll and that UFOs like to land in rural farming areas and make beautiful art out of cornfields without ever being seen at 2 AM, and that Big Foot has a penchant for hiding in the woods and never leaving) because where is the conspiracy? Almost all statins are generically available today and have dramatically reduced the cost of health care by reducing the need to be treated in a hospital for a major procedure.

Where is the real conspiracy? I will tell you my problem with statins and what the real conspiracy should be – there are too many people on high doses of these drugs that could be on a lower dose or no statin at all if they changed their lifestyle. And, in these future clinical trials of statins we need to start adding a basic lifestyle change intervention as a comparative group. I really wonder what would have happened if the statin group

went up against 5-10% body weight loss plus a regular exercise group instead of placebo. That would have been awesome and I am NOT confident that statins would have beat this group but who knows because this has never been done in a major trial of statins! This is the real major conspiracy so bring on Big Foot! He (or is it she?) has to be real old now and probably needs a statin, some new shoes and arguably a shower because this poor dude has been running and escaping from cameras his whole life! Just ask the Loch Ness monster and Abominable Snowman or Elvis because I saw all three of them yesterday near my house having a cappuccino with Jimmy Hoffa!

Reference

1. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*, 2 April 2016, Epub.

Prostate Cancer Detection from Urine RNA Steps Closer

Testing for non-coding RNA molecules in urine may offer a way to detect prostate cancer that is more accurate and reliable than current methods using biomarkers such as PSA and PCA3. The researchers believe using non-coding RNAs as biomarkers will lead to more reliable and accurate tests for prostate cancer than the current PSA test.

This was the conclusion of a German study presented on March 11-15, 2016, at the European Association of Urology Congress (EAU16) in Munich, Germany, by Friedemann Horn, a professor in the University of Leipzig and

the Fraunhofer Institute for Cell Therapy and Immunology IZI, and Manfred Wirth, a professor in the University of Dresden. Both researchers led the work.

Progress in genomic science is revealing that genetic programming in human beings and other higher organisms is far more intricate and complicated than we thought. It appears our bodies express a huge repertoire of previously overlooked molecules that orchestrate a hidden layer of genetic signals involved in health and disease.

One group of these genetic molecules is non-coding RNA

(ribonucleic acid). RNAs are molecules that help to read and translate DNA (deoxyribonucleic acid) to make proteins – the workhorses of cells. Until recently, it was thought that many RNAs that do not help make proteins – called non-coding RNAs – were simply "junk" and had no particular function.

Now, greater understanding of non-coding RNAs reveals they help control many biological processes, including the development and progression of cancer, and measuring them could offer a way to detect disease. Current biomarker tests for

prostate cancer measure levels of PSA and PCA3, but they are not particularly accurate and can either miss many cancers or produce false positives.

The researchers behind the new study have identified a series of non-coding RNA molecules that could potentially be combined into a single urine test to detect prostate cancer. A combined test could offer greater sensitivity and specificity than the current biomarker tests and thus make population screening much more viable.

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Radiation-Hormone Combo *(Continued from page 1)*

from 37 centers in 14 countries. With participants staged by tumor status, PSA/Gleason score and having no nodal or metastatic involvement, 74.8% of the cohort had intermediate-risk disease and 24.8% had high-risk disease. They were randomized to RT at 70, 74, or 78 Gy or RT plus goserelin ADT.

The authors noted that up to 30% of men who have RT alone for intermediate- or high-risk localized prostate cancer relapse biochemically within five years. In this study, however, the five-year cumulative local relapse rate was 6.6% (95% CI 4.1-9.1%) in the RT arm vs. 2.1% (95% CI 0.7-3.6%) in the combination arm, for a competing risk adjusted HR of 0.37 (95% CI 0.21-0.68, $P=0.001$). Distant metastases occurred in 31 of 409 men (7.6%) in the RT group and 18 of 410 patients (4.4%) in the combination group ($P=0.05$).

Bolla and associates noted that the D'Amico trial had looked at conventional radiation (70 Gy) combined with six-month complete ADT for men with intermediate- and high-risk prostate cancer and showed an increased eight-year overall survival ($P=0.01$). They also observed that newer techniques such as daily image-guided intensity-modulated RT have enabled the safe delivery of high doses to the prostate and pelvic nodes and may soon be combined with brachytherapy or hypofractionation.

Sumanta Pal, MD, of City of Hope Comprehensive Cancer Center in Duarte, CA, told *MedPage Today*, "For the spectrum of men included in this study ... it appears that a short course of hormones added to RT results in a dramatic improvement in clinical outcome." He cautioned, however, that it remains to

be seen if this approach improves overall survival.

"The side effects of hormone therapy are not insignificant," said Pal, who was not involved with the study. "It will be interesting to see if this data swings the pendulum for men deciding between RT and surgery for intermediate- and high-risk prostate cancer."

In an accompanying JCO editorial, the University of Miami's Alan Pollack, MD, PhD, and Matthew Abramowitz, MD, said the study expands the body of knowledge about the efficacy of short-term ADT plus RT, with its finding of an overall five-year bDFS rate of 83% for ADT vs. 70% without ADT. "The 10-year survival rates appear to be more pronounced, with further separation of the curves," Pollack wrote, also noting the statistically significant benefit from ADT in clinical [P]FS.

Addressing the "interesting" dose-escalation component of the trial, Pollack and associates wrote, "The balance between the use of AST [AS therapy] and RT dose is a topic of much interest. However, as the investigators point out, this is an exploratory subgroup analysis. At each dose level, the benefit of AST was maintained; yet, in the multi-variable analyses described, no significant interaction was found with external beam RT [EBRT] dose."

The commentators wrote: "Evidence at hand strongly supports the use of ADT and EBRT for men with intermediate- to high-risk prostate cancer." The morbidity of short-term ADT, however, remains a concern in treatment decisions. "Eliminating ADT is highly desirable, but not advisable, for the vast majority of such patients."

MedPage Today
29 March 2016

PSA Screening Publications Influence Biopsy Rates and Associated Complications

While absolute rates of biopsy and post-biopsy complications have decreased following several benchmark PSA screening publications, the relative risk for each patient continues to increase, according to a new study by Mayo Clinic researchers. The study is the largest to examine the impact of PSA screening trials and revised PSA screening guidelines on rates of prostate biopsy and the first to examine their impact on post-biopsy complications. The results, which appear in *European Urology*, suggest a need to reduce the harm associated with biopsy.

"The recent guidelines urge that we are more thoughtful in our approach to PSA screening, and a downstream effect of that seems to be that we biopsy fewer patients, which has reduced the overall number of patients who experience biopsy-related complications," says R. Jeffrey Karnes, MD, a urologist at Mayo Clinic and senior author of the study. "But, we also found that the potential complications per patient went up, which means that we must continue to take steps to make biopsies as safe as possible."

Prostate biopsy and post-biopsy complications represent important risks of PSA testing, which screens for men with abnormally high levels of PSA in their blood. Although large randomized trials and updated guidelines have challenged routine PSA screening, it is unclear what kind of an impact these publications have had on biopsy or post-biopsy complications. In this study, Dr. Karnes and his colleagues sought to determine how the rates of biopsy or post-biopsy complications have changed following the publication of:

- 2008 and 2012 US Preventive Services Task Force (USPSTF) recommendations
- 2009 European Randomized Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial
- 2013 American Urological Association (AUA) guidelines

Because little research has been done on biopsy complications, they also looked for factors that seem to put specific patients at higher risk.

The researchers analyzed administrative claims data from the OptumLabs™ Data Warehouse, which contains information on more than 100 million individuals enrolled in private health plans and Medicare Advantage Plans across the US. They focused specifically on data from 104,584 men over 40 who underwent biopsies between Jan. 1, 2005, and Sept. 30, 2014.

Over that time, researchers found that biopsy rates fell by one-third, with significant drops following the 2008 USPSTF recommendations and 2012 and 2013 AUA guidelines. Approximately 17% of biopsies resulted in complications, the most common of which included infections, bleeding and urinary retention. Overall, complication rates fell by 10%. However, the complication rate in individuals increased from 14-18%, mostly due to infection. Given this increase in relative risk, Dr. Karnes and his colleagues performed statistical analysis to identify predictors of post-biopsy complications. Patients who were over 70 and had a prior diagnosis of

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Saturation Prostate Biopsy Not Better

Unusual tumor location outside of biopsy grids, such the anterior lobes, apex, bladder neck, and parasagittal zones, is among the main reasons for missing high Gleason grade tumors, a finding that supports the need for improved detection methods, such as MRI-guided targeted biopsy, a research team led by Huihui Ye, MD, of Beth Israel Deaconess Medical Center in Boston, reported online ahead of print in *Urology*.

Dr. Ye's group compared the diagnostic accuracy of the standard 12-core prostate biopsy and saturation biopsy (18–33 cores, median 20) among 375 consecutive patients who underwent radical prostatectomy (RP). Of these, 269 had 12-core biopsies and 106 had saturation biopsies. Findings on biopsy and final pathology were compared.

A similar proportion of men in each group had high Gleason grade tumors on biopsy (49.1 vs. 50%) at RP (69.5 vs. 65.1%). Among men with high Gleason grades on final pathology, 12-core and saturation biopsies had comparable sensitivity, specificity, and negative and positive predictive values (69.5, 97.6, 58.4 and 98.5% vs. 72.5, 91.9, 64.2, and 94.3%, respectively) in detecting high Gleason grades. On multivariate analysis, pre-biopsy serum PSA level and clinical T stage (cT2 vs. cT1) independently predicted Gleason upgrading. Saturation biopsy was not a significant predictor.

The study was limited by data generated at a single tertiary-care academic hospital and most men with PCA were treated by four urologists. "Therefore, our study results may not be representative of other urological

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Can a Blood Test Predict Aggressiveness of Prostate Cancer before Surgery?

The success of prostate cancer surgery depends on a variety of factors. Now a new study from scientists in Milan has shown that for local prostate cancers treated with radical prostatectomy (RP), you can preoperatively predict the aggressiveness of the disease, via a simple blood test.

When describing prostate cancer, urologists normally use the Gleason pattern. Gleason pattern one means that the cells in the tissue are normal, whereas Gleason pattern five (the highest score) indicates that the tissue is largely taken over by tumour cells. If a patient has Gleason pattern five, then the predicted outcomes are poor.

Now a group of Italian researchers have been able to show that hypogonadism (which is low levels of the sex hormone testosterone) predicts a high Gleason score. A group led by Dr. Marco Mos-

chini (San Raffaele Hospital, Milan) retrospectively correlated hormone levels and Gleason scores in 1,017 men who underwent RP at the San Raffaele hospital in Milan.

Of these, 118 men showed Gleason pattern five. After adjusting for age, they found that testosterone and sex-hormone-binding globulin (SHBG) blood levels were able to predict men with Gleason pattern 5 (Odds Ratio = 1.79, $p=0.025$). Dr. Moschini stated "this association will allow us to predict what the outcome will be before we decide to treat a patient with surgery. Potentially this can be helpful to identify patients with the most aggressive prostate cancer before surgery."

"There is an urgent need for new research to uncover the role which hormones play in prostate cancer development. What we don't yet know is if this is an associa-

tion, or if hypogonadism in some way increases the risk of developing high-grade prostate cancer. If this is the case, then it may be that treating the hypogonadism can lessen this risk, but we need more work before we can be sure of that."

Professor Alexandre de la Taille (Paris), a member of EAU Scientific Congress Committee, and who was not involved in the research commented: "Several reports in the literature mention that a low serum testosterone level is associated with prostate cancer aggressiveness. This study highlights the fact that SHBG is also linked to high Gleason score. These cancers, developed in this special hormonal environment, are probably due to different molecular pathways and represent a new field to explore."

*Medical News Today
11 March 2016*

US Lawmakers Want Health Agencies to Lower Drug Cost for Prostate Cancer

A group of lawmakers is calling on the National Institutes of Health and Department of Health and Human Services to step in and reduce the cost of Medivation Inc.'s and Astellas Pharma Inc.'s prostate cancer drug Xtandi® (enzalutamide).

In the letter signed by Democratic US presidential candidate Bernie Sanders and Reps. Lloyd Doggett (D-TX) and Peter Welch (D-VT), the lawmakers urged NIH to hold a public hearing to consider overriding the patent on Xtandi to make the drug available at a lower price.

The medication has an average wholesale price in the United States of more than \$129,000 but is sold in Japan

and Sweden for \$39,000 and in Canada for \$30,000, according to the lawmakers' letter. They noted federal funds supported development of the drug, which was based on research at the University of California, Los Angeles, conducted with taxpayer-supported grants. The drug costs four times more in the United States than in other major countries, the lawmakers wrote in the letter, addressed to HHS Secretary Sylvia Burwell and NIH Director Francis Collins.

"When Americans pay for research that leads to a pharmaceutical, that drug should be available at a reasonable price," said Doggett, co-chair of the House Democratic Caucus Prescription Drug Task

Force. "An unaffordable drug is 100 percent ineffective."

A spokesman for Astellas did not have an immediate comment on the lawmakers' letter or the cost of Xtandi. Medivation could not be reached for comment. Spokesmen for the NIH and HHS could not be reached.

US lawmakers and presidential candidates have in recent months stepped up criticism of US drug price trends, raising investor concerns that future price cuts could hurt pharmaceutical and biotech companies.

"The United States government should use every tool available to lower outrageously high prescription

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New Target Makes End Run against Therapy-Resistant Prostate Cancer

UC Davis researchers in collaboration with the other institutions found that suppressing the nuclear receptor protein ROR- γ with small-molecule agents can reduce androgen receptor (AR) levels in castration-resistant prostate cancer (CRPC) and stop tumor growth.

This novel approach does not directly target the AR, but rather inhibits the gene that codes for the AR protein. Reducing AR levels could help men overcome CRPC and even rescue existing therapies. The research was published in the prestigious journal *Nature Medicine*.

"This is a new target and a totally new way of hitting prostate cancer," said Hongwu Chen, a professor in the Department of Biochemistry and Molecular Medicine and lead author on the paper. "This strategy targets the root cause of the problem – the overexpression of the AR gene and its protein."

In the vast majority of prostate cancers, the AR gene becomes hyperactive, driving

tumor growth and metastasis. Antiandrogen therapies can slow, and even stop, prostate cancer for a time. But quite often the gene mutates to resist the treatment.

However, suppressing ROR- γ circumvents this resistance. Because the protein is required for AR gene expression, ROR- γ inhibition strongly reduces AR protein levels in tumor cells. By preventing AR protein synthesis, ROR- γ antagonists can potentially short-circuit the resistance process.

"Essentially all existing therapies work on blocking either activation of the AR or the genes it regulates," said Christopher P. Evans, professor and chairman of the Department of Urology and a co-author of the study.

"However, as patients become resistant to existing agents, the AR becomes mutated, amplified and spliced. This (ROR- γ suppression) mechanism blocks the actual expression of the AR and its spliced forms."

To illuminate the relationship between ROR- γ and the AR

gene, Chen's team studied a number of small molecule ROR- γ antagonists, both in cell lines and human tumors in mice. In each model, suppressing ROR- γ reduced AR gene expression and AR protein levels, blocking tumor growth. These inhibitors showed broad effectiveness, inhibiting several AR variants, including AR-V7, which has been linked to resistance to enzalutamide and abiraterone in men with advanced disease.

"Blocking ROR- γ re-sensitizes castration-resistant prostate cancer to drugs that directly inhibit AR pathway signaling, such as enzalutamide," said Evans. "A combination approach can potentially be very effective." In addition to reducing AR levels, ROR- γ suppression also can reduce the prevalence of several known oncogenes.

"ROR- γ suppression is quite remarkable," said the study's first author, Junjian Wang, a project scientist in the Department of Biochemistry and Molecular Medicine. "It can reduce levels of ERG and MYC, which are known to drive prostate cancer."

While ROR- γ was neglected in cancer research, it has been widely targeted for autoimmune diseases. As a result, there are a number of ROR- γ antagonists in the pipeline. "ROR- γ has been extensively studied as a target for rheumatoid arthritis, inflammatory bowel disease, psoriasis and other autoimmune conditions," noted Chen.

"Some of the drugs are orally available and have been found to be safe in early clinical trials. They could be a great help for patients with advanced prostate cancer."

Medical News Today
29 March 2016

Biopsy Rates

(Continued from page 4)

cancer or a history of fluoroquinolone antibiotics or anti-coagulant use were found to be at highest risk. Researchers believe that the recognition of these modifiable and non-modifiable risk factors could guide future decision-making for patients and clinicians considering a biopsy.

"Our findings indicate that we should focus further efforts on improving how we select patients to undergo a biopsy, how we prep them and, perhaps, even how we perform biopsies to reduce the complications associated with the procedure," says Dr. Karnes.

Medical News Today
1 April 2016

Drug Cost

(Continued from page 5)

drug prices," Sanders said. "NIH has the power to stop this blatant profiteering and put the pharmaceutical industry on notice that the era of charging unconscionable prices must end."

Also signing the letter were Sens. Al Franken (D-MN), Sheldon Whitehouse (D-RI), Amy Klobuchar (D-MN), Patrick Leahy (D-VT) and Elizabeth Warren (D-MA), as well as Reps. Elijah Cummings (D-MD), Jan Schakowsky (D-IL), Rosa DeLauro (D-CT) and Mark Pocan (D-WI).

Reuters Health Information, 30 March 2016

Urine RNA Testing (Continued from page 3)

A test with high [sensitivity] is good at ruling in disease when the result is positive. A test with high [specificity] is good at ruling out disease when the result is negative.

For their study, the researchers took 64 prostate cancer tissue samples obtained from biopsies and read 200 million sequences in genetic molecules from each sample. They found over 2,000 sequences that were significantly different in tumor samples than in healthy controls. Some of these sequences were for non-coding RNAs that showed better specificity and sensitivity than established

prostate cancer markers. The new biomarkers were also found to be present in urine samples from prostate cancer patients, and initial tests suggest they offer a precise way to detect the disease.

Professor Wirth stated that one of the non-coding RNAs – called tumor-associated proliferation-inducing RNA (TAPIR) – also showed significant promise in stopping cancer cell growth. However, the team says it is too soon to say whether this result will prove to be clinically useful.

EAU16 news release
13 March 2016



Doctor Chodak's Bottom Line *(Page number and first few words of article title)*

Gerald Chodak, MD, Author, *Winning the Battle Against Prostate Cancer*, Second Edition <http://www.prostatevideos.com/>

Editor's Note: Us TOO has invited certain physicians and others to provide information and commentary for the *Hot SHEET* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

P1 – “Radiation Hormone”

Progress continues in the management of intermediate- and high-risk prostate cancer when treated by radiation therapy (RT). Bolla and co-workers recently presented their results of an ongoing randomized trial in which men with intermediate- or high-risk localized disease received either RT alone at variable doses of 70, 74, or 78 Gy or combined with androgen deprivation therapy (ADT) using an LHRH agonist for six months. The early findings are that both biochemical disease-free survival and progression-free survival are significantly improved with the combination approach with about one man benefitting out of every six treated. Thus far, however, survival has not been affected. A previous randomized study by D'Amico et al showed that six months of ADT improved survival for men with intermediate-risk disease. In the current study, 75% of the men had intermediate-risk disease and only 25% of the group had high-risk disease. Unfortunately, the results were not stratified by risk groups. Therefore it is unclear whether high-risk patients will benefit with this duration of therapy, especially because other studies for Stage T3 disease failed to show a benefit with four or six months of ADT. Another problem is that three doses of RT were used and it was left to the doctor to decide rather than being determined by randomization. This could have some effect on interpretation of the results. For these reasons, the final results could be misleading.

The Bottom Line: More time and subset analysis are needed to determine if six months

of ADT will be enough to improve survival for men with high-risk prostate cancer.

P1 – “For Prostate Cancer”

Another report on RT by Den and co-workers provides interesting and potentially important information about the optimal dose for treating localized disease. They conducted a meta-analysis of randomized trials and found that using higher RT doses did not translate into better survival even though it did produce better PSA responses. There are two important implications of these findings. First, as I have said over and over again in this column, PSA IS NOT A RELIABLE SURROGATE OUTCOME FOR MEN TREATED WITH RT. This is so important because of all the short-term studies that get published with comparative results based solely on PSA. The message to patients is they should not trust that a PSA provides real proof that a treatment is as effective as the effectiveness of a treatment based on survival. The second message is that men should inquire about the rationale for the RT dose being recommended to them. It is clearly good for the doctor to use more RT, but it now seems that more may not be better for the patient. The good news, however, is that it does seem safe with current techniques being used without significantly raising the incidence of side effects.

The Bottom Line: Raising the dose of external RT is not translating into better survival. Also, PSA is not a reliable surrogate to predict survival for men treated with RT.

P1 – “Economic Analysis”

Screening recommendations have varied from ‘don't do it' to ‘do it routinely' and both

approaches have significant problems. Now, Etzioni et al have performed some mathematical analyses to determine if a modified approach could be worthwhile. They analyzed different approaches starting at age 40 that included no immediate treatment for Gleason 7 and below without first having clinical progression. The analysis found that some strategies can prove to be cost effective and save lives, however, it would mean not treating many men after they are diagnosed with cancer. It also means not doing a biopsy unless the PSA is above 10 ng/mL or it exceeds an age-specific range. One eventual problem is the frequency that both doctors and patients will accept the recommendation. If they choose not to follow this advice and take a different approach, both the cost effectiveness and the number of men benefitting versus being harmed by side effects and unnecessary therapy will change. Nevertheless, work will continue to find the best way to approach this problem of balancing risk vs. benefit.

The Bottom Line: Efforts continue to find a compromise approach to screening balancing the risks and benefits.

P2 – “Meta-Analysis” It has been abundantly clear for some time that prostate cancer is a very diverse disease. The more we understand the subtleties of determining which patients respond or don't respond to a therapy, the better doctors can specifically tailor therapies. The meta-analysis by Halibi et al identifies different outcomes for men with different sites of metastatic disease with the worst survival occurring

in men with liver metastases. This is a first step in designing clinical trials because it means they need to stratify patients according to the different risk factors. Hopefully such studies will be forthcoming.

The Bottom Line: Men with metastatic prostate cancer have varying outcomes depending on the site of disease. This information can be used to design and analyze future clinical studies.

P2 – “Enzalutamide Broadly”

Evans and co-workers provide a good example of this variability in responsiveness. They conducted a subset analysis of the results from the PREVAIL TRIAL, which used enzalutamide to treat metastatic castrate resistant prostate cancer (mCRPC). Previous studies showed that this drug improved survival when given prior to docetaxel chemotherapy. This new analysis found that it significantly improved survival in men with low- or high-volume bone metastases, lymph node metastases and visceral and non-visceral metastases, but the effectiveness varied depending on the metastatic site. Knowing the response rate varies for these sub-groups means that future studies that combine other therapies with enzalutamide also will need to stratify enrollment according to these factors.

The Bottom Line: Enzalutamide improves survival of men with mCRPC but knowing that the response varies depending on the extent and location of metastases provides an opportunity to evaluate new combination therapies for each subgroup.

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RT Dose & Survival

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metastases, among other measures, did not improve. "It's important to check our assumptions," says Adam Dicker, chair of radiation oncology at the Sidney Kimmel Medical College of Thomas Jefferson University. "This study suggests that our reliance on the PSA test as a proxy for patient outcomes may not as useful as many researchers thought, which has broad implications for the design of future clinical trials and the interpretation of current and previous studies."

Dr. Den's study also demonstrated that increasing RT dosage was not associated with worse treatment toxicity, suggesting that current treatment practices are safe. "These data suggest that other therapies may be needed with RT to increase survival," says Dr. Den.

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The Bottom Line (Continued from page 7)

P3 – "Prostate Cancer" Can measuring non-coding DNA molecules eventually lead to a urine test for prostate cancer that is superior to PSA or PCA3? Some preliminary data suggest it might be possible, but more research is needed before one can begin to substitute such a test for either of the other markers. PSA was widely adopted based on similar preliminary excitement without knowing its true impact on survival. It is hoped that the right studies are done with new markers so that a similar mistake is not repeated. One of the problems will be how often it detects non-life threatening disease. The only way to know if the marker is worthwhile is to conduct another lengthy randomized trial.

The Bottom Line: Non-coding DNA molecules hold some promise as a new way to screen for prostate cancer but much more work is needed to make that determination.

P4 – "PSA Screening" Morbidity from prostate biopsy is one of the problems associated with routine screening. Karnes et al analyzed insurance information from more than 100,000 men and found that the rate of screening decreased from 2005-2014 but individual infections increased. The answer is not obvious, but it is unlikely due to lack of experience of urologists performing the biopsy. One likely possibility is that antibiotic overuse may have led to more resistant organisms, so that men receiving typical antibiotics prophylaxis are not adequately protected from infection. Regardless, it also means that it is another problem with routine screening for this disease that cannot be ignored.

The Bottom Line: Although the infection rate has gone down overall, the individual rate of infections has increased. The question is why and more studies are needed to address this issue.

Saturation Biopsy

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practices, particularly private practice and community hospitals," researchers noted. In addition, the saturation biopsy approach was performed by a single urologist, whereas 12-core biopsies were performed by many urologists.

Judd W. Moul, MD, the James H. Semans Professor of Surgery at Duke University Medical Center and director of the Duke Prostate Center, in Durham, NC was not involved in the study but was asked to comment on it.

He noted that Gleason 6 tumors were upgraded at RP by about 40% regardless of the type of biopsy. "The authors use these data to suggest that prostate MRI may improve the selection for active surveillance (AS)," Dr. Moul said. "However, prostate MRI has yet to be proven prospectively to help improve the care of our AS patients."

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